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Lewis J Kreisler
Legal Department
930 Clopper road
Gaithersburg, MD 20878

EXAMINER	
ZEMAN, ROBERT A	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/664,444
Filing Date: September 18, 2000
Appellant(s): BELL ET AL.

Douglas A. Golightly
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 15, 2009 appealing from the Office action mailed July 16, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Jain (Scientific American Vol. 271 No. 1, pages 58-65, July 1994).

Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4).

Dermer (Bio/Technology, 1994, Vol. 12 page 320).

Gura (Science, Vol. 278, 1997 pages 1041-1042).

Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290).

Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836).

Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239).

Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776).

Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857).

Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

I. Rejection under 35 U.S.C. 112, first paragraph, for failing to meet the enablement requirements without a biological deposit

Claims 27-31 and 73-77 are rejected under 35 U.S.C. 112, first paragraph, for failing to meet the biological deposit requirements.

It is apparent that the VSV strains M1, M2, M3, M4 and M5 are required in order to practice the invention. The deposit of biological organisms is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)).

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be

irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

II. Enablement Rejection under 35 U.S.C. 112, first paragraph

Claims 1, 6-13, 19, 24-37, 64-77 and 79-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods utilizing attenuated VSV for reducing the viability of hematopoietic tumor cells *in vitro* and the use of attenuated VSV to reduce the viability of tumor cell based xenographs in immunodeficient mice, does not reasonably provide enablement for the utilization attenuated VSV for the reduction of viability of all types of hemapoietic tumor cells to reduce the viability of a tumor cell in an immunocompetent animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Appellant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of reducing the viability of hemapoietic tumor cells by administering an attenuated strain of VSV to said melanoma tumor cells. Said melanoma tumor cells can optionally be leukemia cells or myeloma (claims 6-13),

have no PKR activity and/or have no STAT1 activity (claim 19). Said VSV virus can be unable to inactivate tumor cell PKR activity (claim 25), or may constitute strains M1-M5 (claims 27-31, respectively). Said method encompasses methods of "treating" tumor cells which reside in a mammalian host. Said method may include the optional administration of interferon prior to the administration of the virus (claims 24 and 37).

Breadth of the claims: The claims are extremely broad in that they encompass literally any attenuated VSV strain. Moreover, the instant claims encompass both *in vivo* and *in vitro* applications. It should be noted that all the instant claims read on the *in vivo* treatment of hemapoietic tumor cells in humans.

Guidance of the specification/The existence of working examples: To use the invention as claimed one must be able to differentially infect a susceptible tumor cell resulting in a reduction in said cell's viability. While the specification provides great detail on the susceptibility of different cell types to VSV and the protective effect of alpha interferon against VSV infection, the specification is silent on the what viruses other than VSV would induce the claimed anti-tumor effect. Additionally, the instant claims are drawn to all forms of hematopoietic tumor cells, while the specification has demonstrated only two leukemia cell lines (MD7E and L1210), a couple of AML cell lines OCI/AML3 and AML5, one CML cell line (K-562) and a T-cell leukemia (MOLT-4) that are that are susceptible to VSV infection. VSV was shown to reduce the viability of only the AML, CML and T-cell leukemia cell lines.

The specification is silent on what receptor is utilized by VSV (or any other virus) for cell entry or which cell types would be able to support a productive viral infection making it difficult to determine if a given tumor cell would be susceptible to the oncolytic properties of VSV or be used as a suitable delivery vehicle. Moreover, the specification is equally silent on what other melanoma tumor cell types are killed by VSV infection. The invention seems to be predicated on the susceptible tumor cells lacking PKR activity, but the specification is silent on which melanoma tumor cells lack said function.

State of the art: At the time of Appellants' invention the art of using oncolytic viruses to treat melanomas was underdeveloped. While the use of oncolytic viruses has been known in the art for decades, said oncolytic viruses were limited, to viruses that would be considered human pathogens.

Predictability of the art and the amount of experimentation necessary:

People of skill in the art require evidence that a benefit can be derived by the therapeutic application of a given substance; however, a survey of the relevant art does not indicate that substances such as those claimed provide such benefit. The instant specification fails to provide significant direction on which viruses, if any, are capable of eliciting a therapeutic response (tumor cell death) when administered to an immunocompetent subject in need. Moreover, the specification is equally silent on how said viruses are to be administered to said subject. Jain discloses known barriers to the delivery of drugs into solid tumors (Scientific American Vol. 271 No. 1, pages 58-65, July 1994). Impediments to drug delivery include: (1) Non-uniform blood

delivery to all areas of the rumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61) and (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1). Consequently, the method of administration would vary depending on the tumor cell type and location of said tumor. Unfortunately, the specification fails to provide guidance to how a given virus should be administered when treating a given hemapoietic cancer. The specification illustrates this point on page 33 where it states that PKR-/- mice were killed with VSV by several routes of infection but that these mice were not affected by intravenous injections of the virus. Moreover, there is a marked difference in the efficacy of delivering a therapeutic agent to a solid tumor cell as opposed to a leukemia cell.

The specification teaches how to use VSV to reduce the viability of melanoma cell lines injected into immunodeficient mice to form xenographs and provides *in vitro* data showing effects of VSV infection on a several hematopoietic cell lines (either with or without alpha interferon). However, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to "treat" hematopoietic tumor cells, although *in vivo* use is clearly encompassed by the claims. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* and xenograft data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals without undue experimentation. Moreover, while those of skill in the

art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo.* These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo.* Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro).* Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and

differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature 'for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Additionally, it should be noted that Example 25 is insufficient to provide enablement for the full breadth of the instant claims. Firstly, the xenographs utilized in Example 25 (on page 50 of the specification), comprise a melanoma derived cell line (SK-MEL3). Secondly, said example only utilizes two of the five VSV mutants disclosed in the instant specification suggesting that the anti-tumor effect of the disclosed VSV mutants is unpredictable. Thirdly, the instant claims are drawn to use of VSV to reduce the viability of all types of melanoma tumor cells whereas Example 25 demonstrates only that two mutated VSV viruses can reduce the viability of cell-line based xenographs in immunodeficient mice. This cannot be extrapolated to the use of wild-type (non-mutated) VSV against established tumors in an immunocompetent animal. Gura (Science, Vol. 278, 1997 pages 1041-1042) teach that xenographs are not good models for determining the efficacy of a treatment modality since "xenograft tumors don't behave like naturally occurring tumors in humans" (see column 2). Gura illustrates the lack of correlation between efficacy in xenograft model systems and in vivo efficacy in humans when she states that the use of xenografts led them to discover "compounds that were good mouse drugs rather than good human drugs" (see the bottom of column 2 on page 1041).

Moreover, on the basis of experimentation performed using an animal model, the specification asserts the invention can be used to treat cancer (hemapoietic). The problem with accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer "vaccines" to attenuate cancer has been met with very little success. In addition to references cited in preceding Office actions, which also describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunization can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather,

the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Moreover, as noted in preceding Office action, Gura (of record) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

With further regard to the predictive value of various different preclinical models, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; 95 (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Appellant has argued that the use of xenografts in mice for evaluating therapeutic efficacy of drugs for treating humans is well established; agreeably the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen. Schuh (*Toxicologic Pathology*. 2004; 32 (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations

towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; 40 (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotropic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; 40: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the

claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). **The MPEP further states that physiological activity can be considered inherently unpredictable.** Thus, Appellant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

Consequently, the specification while being enabling for methods utilizing VSV for reducing the viability of hematopoietic tumor cells *in vitro* and the use of VSV to reduce the viability of tumor cell based xenografts in immunodeficient mice, does not reasonably provide enablement for the utilization VSV for the reduction of viability of a hematopoietic tumor cell in an immunocompetent animal. The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

(10) Response to Argument

I. Rejection under 35 U.S.C. 112, first paragraph, for failing to meet the enablement requirements without a biological deposit

Appellant argues:

1. The Examiner has not provided reasons why deposits are necessary for the enablement of the instant claims.

2. Appellant has presented arguments that provide a *prima facie* showing that the claimed VSV strains are well known and available to the public.

3. Appellant has provided multiple peer-review journal articles utilizing the claimed VSV strains.

4. Many scientific journals require that their authors to make biological materials available to the research community.

5. The instant specification provides both the amino acid and nucleic acids sequences for the claimed VSV strains thus enabling the skilled artisan to make said strains.

Examiner Rebuts

With regard to Point 1, the Examiner clearly points out on page 4 of the Final Office action mailed on 7-16-2008, that the recited VSV strains are required in order to practice the claimed invention.

With regard to Points 2-4, while Appellant has demonstrated that the claimed VSV strains are known in the art, Appellant has failed to demonstrate that said strains are available **without restriction**. Appellant's arguments illustrate that restrictions apply to the public

availability. For instance, the Journal of Virology only requires that a "biological" be made "available in a timely fashion and at a reasonable cost to member of the scientific community for non-commercial purposes." (see page 11 of the instant Appeal Brief).

With regard to Point 5, the instant specification does not disclose the sequence for the entire genomes of the recited VSV strains. The portions of the specification and drawings cited by Appellant (Table 11, Example 27, Figures 14-22 and the sequence listing) disclose the sequences of various viral proteins. Consequently, contrary to Appellant's assertion, the skilled artisan cannot "make" the recited VSV strains.

II. Enablement Rejection under 35 U.S.C. 112, first paragraph

Appellant argues:

1. The instant claims relate to "reducing the viability of a tumor cell" and as such don't require any "efficacy" or "therapeutic effect". What is pertinent is whether one of skill in the art can reduce the viability of a hematopoietic tumor cell with the administration of VSV.

1. The Examiner has not provided reasons for doubting that one skilled in the art could reduce the viability of hematopoietic cells *in vitro* or *in vivo* using the claimed methods.

2. The rejection focuses on enabling support for "*in vivo* treatment of hematopoietic tumor cells in humans" and not "reducing the viability of a hematopoietic tumor cell(s)".

3. The instant claims relate to "reducing the viability of a tumor cell" and as such don't require any "efficacy" or "therapeutic effect". What is pertinent is whether one of skill in the art can reduce the viability of a hematopoietic tumor cell with the administration of VSV. There is no limitation to "treat cancer" in the instant claims.

4. The BPAI decisions in *Ex parte* Boutin and *Ex parte* Saito and Zhao both stand for the proposition that unless the claims explicitly refer to a therapeutic benefit, typically, the examiner should not determine if the claims are enabled for an unclaimed therapeutic benefit. The clinical response is not pertinent for meeting the enablement requirement with regard to the claimed invention.

5. *Ex parte* Ayishi is similar to the present case in that the claims do not specifically recite or require a therapeutic effect, in said decision the Board stated that "when the claims are not limited to a method that achieves therapeutic or clinical efficacy, such efficacy is not required for the claims to be enabled.

6. Both Kelland et al. and Peterson et al. conclude that xenograft models are predictive of clinical outcome and hence support a conclusion that the claimed invention is enabled.

7. McCormick (U.S. Patent 5,677,178) and Pecora et al. (Journal of Clinical Oncology 20(9):2251-2266) demonstrate that *in vitro* and *in vivo* xenograft models reasonably correlate with clinical results.

8. The post filing articles by Lichty et al., Cesaire et al., Porosnicu et al., Balachandran and Barber, Stojdl et al. (2003) and Stojdl et al. (2000) provide evidence that the skilled artisan would have been enabled to use the presently claimed methods for reducing the viability of tumor cells by administering VSV.

9. Kelland clearly supports the position that one of skill in the art would conclude that the models and related results, described in the instant specification, reasonably correlate with an expected similar result in other animals, such as humans.

10. Appellant does not understand the relevance of Wang et al. as it relates to T-cell directed cancer vaccines.

11. Gura discusses historical results in a general and broad sense and does not speak to the predictive value of models related to evaluating the administration of a virus to a tumor cell.

12. Voskoglou-Nomikos et al. proves no evidence as to whether *in vitro* or *in vivo* experiments related to administering a VSV virus to hematopoietic tumor cells reasonably correlate to expected results in other animals.

13. Saijo focuses on whether the results of preclinical studies for molecular-target-based drugs correlate with results in clinical trials and does not have any particular relevance to methods of reducing the viability of hematopoietic tumor cells by administering VSV.

14. Schuh states that the lack of correlation between mouse models and results in clinical trials is the reliance on a single model. Since Appellant has demonstrated efficacy in multiple mouse models, the skilled artisan would necessarily expect those results to correlate with results expected in a human.

15. Bibby clearly stands for the proposition that with regards to leukemias "there is a general misconception that tumours in rodents are sensitive to drug therapy and easy to cure". Therefore the skilled artisan would conclude that methods resulting in the reduction of the viability of hematopoietic tumor cells in a rodent would reasonably correlate with results in a human.

16. Peterson et al. does not teach that results in xenograft models does not correlate with clinical results in another animal or human and hence Appellant is unclear as to the relevance of Peterson et al.

17. There is ample data supporting the claim that hematopoietic cancers are, in general, appropriate targets for VSV as evidenced by the specification (which disclosed the susceptibility of six different classes of hemapoietic cell lines) and the post filing references which demonstrated the susceptibility of six additional hematopoietic cells lines. Additionally, the specification discloses that the skilled artisan can readily screen a particular tumor cell for susceptibility to VSV.

18. Winograd discloses that there is "a good predictability of a panel of human tumor cell lines for clinically effective drugs."

19. The FDA typically accepts positive tumor xenograft results as a sufficient level of preclinical activity when approving a clinical trial.

20. *In vitro* experiments continue to be used as an initial screening method when identifying treatments for *in vivo* use.

21. In the prosecution of Application 11/685,483 the examiner acknowledges that the use of VSV in cancer treatments is enabled.

Examiner Rebuts

With regard to Point 1, Appellant is reminded that the rejection clearly states that the specification is "enabling for methods utilizing attenuated VSV for reducing the viability of hematopoietic tumor cells *in vitro*". Moreover, the Office action clearly sets forth the Examiner's reasoning with regard to the non-enablement of the *in vivo* embodiments of the instant claims (see pages 9-16 of the previous Office action).

With regard to Point 3, contrary to Appellant's assertion, the reduction in the viability of a tumor cell in the context of a living being (i.e. *in vivo* applications) constitutes a therapeutic effect.

With regard to Points 4 and 5, the BPAI decisions in *Ex parte* Boutin, *Ex parte* Saito and Zhao and *Ex parte* Ayishi are not germane to the instant application as the fact patterns are different (i.e. the instant claims refer to a therapeutic response). Contrary to Appellant's assertion, the reduction in the viability of a tumor cell in the context of a living being (i.e. *in vivo* applications) constitutes a therapeutic effect. Consequently, clinical efficacy is pertinent with regard to the enablement of the instant claims.

With regard to Point 6, the portion of the reference cited by Appellant (page 831 not page 83) is taken out of context as Kelland et al. was summarizing the correlation between xenografts models and hollow fiber based models. Moreover, Kelland, does not advocate the use of a xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not. Moreover, Kelland discloses that the xenograft model is an effective screen for candidates for Phase I clinical trials and contrary to Appellant's assertion does not constitute a predictor of *in vivo* efficacy. Finally, Peterson et al. clearly disclose in the abstract that many agents have shown activity in preclinical models (i.e. *in vitro*, xenografts) but have had minimal activity clinically (see abstract).

With regard to Point 7, McCormick et al. is drawn to gene therapy methods. McCormick et al. administered a replication deficient adenoviruses that lacked both Rb and p53 *in vitro* to

neoplastic cells lacking p53 and/or Rb function (see column 18, line 44 to column 20, line 23). McCormick is silent with regard to *in vivo* efficacy of said method and makes no demonstrations of a correlation between *in vitro* data and *in vivo* efficacy. Pecora et al. deals with the use of Newcastle Disease Virus to "treat" solid tumors in patients. Pecora et al. provides no correlation between *in vitro* data and *in vivo* efficacy. Moreover, as set forth in the rejection response to a given treatment modality is predicated on many things... tumor type, mode of administration, the "treatment" moiety. Pecora et al. is limited to solid tumors and disclose that a multitude of responses to varying tumor types (see page 2259). Moreover, the instant claims encompass a myriad of different cancers including chronic myeloproliferative diseases, myelodysplastic/myeloproliferative diseases, myelodyplastic syndromes, acute myeloid leukemias, B-cell neoplasms, T-cell and NK-cell neoplasms, Hodgkin lymphoma, histiocytic and dendritic cell neoplasms and mastocytosis. The *in vitro* data presented in the instant application is not even representative of the genus of hematopoietic cancers. And as evidenced by Pecora et al., clinical response is very dependent on the cancer type.

With regard to Point 7, the post-filing articles cited by Appellant, demonstrate the *in vitro* efficacy of the use of VSV to reduce the viability of a hematopoietic tumor cell (which has been indicated as being enabled). Moreover, Lichty et al. is limited to the use of IFN-inducing attenuated strain of VSV and cannot be relied upon for all types of VSV. Additionally, even though Lichty et al. was published 5 years after the filing of the instant application, it still refers the *in vivo* use of VSV prophetically (see page 89).

Cesaire et al. is limited to the *in vitro* use of VSV.

Porosnicu et al. deals with the use of replication-competent VSV that has been modified to carry for genes (i.e. for cytokines) [see page 8366]. Additionally, Porosnicu et al. point out that a problem with *in vivo* viral tumor therapy in an immunocompetent host is the host's immune system suppressing the required oncolytic effect (see page 8373). Finally, Porosnicu et al. is silent on the *in vivo* efficacy of VSV-based tumor therapy and provides no correlation between their *in vitro* data and *in vivo* efficacy against hemapoietic malignancies.

Balachandran and Barber are limited to the *in vitro* application of VSV and only prophetically state that VSV might be useful in therapeutic strategies (see abstract). This cannot be construed as provided support for the *in vivo* efficacy of VSV against hematopoietic malignancies.

Stojdl et al. (2000) is limited to *in vitro* use of VSV and its use against melanoma xenographs. Stojdl et al. is silent on the *in vivo* application of VSV. Stojdl et al.'s on comment regarding any clinical consequences of VSV treatment is the *ex vivo* purging of bone marrow cultures for use in autologous bone marrow transplantation (see page 824).

Stojdl et al. (2003) demonstrated *in vitro* efficacy of two mutant VSV strains (AV1 and AV2) and their use in immunocompetent mice. Stojdl et al. also points out oncolytic viruses are rapidly inactivated in the blood and are inhibited by physical barriers.

Given, the large genus of VSV strains (both wild-type and genetically engineered) and the wide range of malignancies encompassed by the instant claims, Appellant's assertion that the cited references provide enablement for the full breadth of the instant claims is unfounded. When looked at closely, said references (post-filing) illustrate the problems associated with viral (VSV) tumor therapy. Given the lack of guidance provided by the specification with regard to how VSV

is to be effectively administered against a given hematopoietic malignancy or even what VSV strain/mutant must be used for a given hematopoietic malignancy and the limited knowledge regard VSV viral therapies in the art (especially with regard to hematopoietic malignancies), the specification is not enabling for the full breadth of the claims.

With regard to Point 9, the portion of the reference cited by Appellant (page 831 not page 83) is taken out of context as Kelland et al. was summarizing the correlation between xenografts models and hollow fiber based models. Moreover, Kelland, does not advocate the use of a xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not. Moreover, Kelland discloses that the xenograft model is an effective screen for candidates for Phase I clinical trials and contrary to Appellant's assertion does not constitute a predictor of *in vivo* efficacy. Finally, Peterson et al. clearly disclose in the abstract that many agents have shown activity in preclinical models (i.e. *in vitro*, xenografts) but have had minimal activity clinically (see abstract).

With regard to Point 10, Wang et al. was cited to illustrate the lack of correlation between *in vitro* success and *in vivo* efficacy in terms of cancer treatments. As pointed out by Wang et al. on page 282 there is "…difficulty in correlating laboratory findings with clinical outcome…".

With regard to Point 11, Gura et al. clearly demonstrates that within the cancer art, xenograft data is not indicative of *in vivo* efficacy since "xenograft tumors don't behave like naturally occurring tumors in humans" (see column 2).

With regard to Point 12, Voskoglou-Nomikos et al. clearly demonstrate that within the cancer art there is not a clear correlation between xenograft models and *in vivo* efficacy and that predictability varies with the models used (as acknowledged by Appellant).

With regard to Point 13, Saijo, like the other references cited by the Examiner, demonstrates that within the cancer art there is not a clear correlation between *in vitro* efficacy and *in vivo* efficacy as illustrated by the high failure rate of molecular-based drugs that had been prescreened in phase I and phase II trials.

With regard to Point 14, Appellant has misconstrued the conclusion set forth in Schuh. Schuh did not state that the use of multiple models would necessarily provide a correlation between mouse model data and clinical efficacy. Schuh clearly states that "preclinical efficacy for anti-tumor therapies should progress through a series of models of increasing sophistication that includes incorporation of genetically engineered animals, and orthotopic and combination therapy models." Such is not the case with regard to the instant specification.

With regard to Point 15, as pointed out by Appellant, that Bibby discloses that leukemias are difficult to treat. Moreover, Bibby deals with the ineffectiveness of conventional murine and xenograft test systems in testing the efficacy of antitumor agents and the need for alternative approaches. Consequently, contrary to Appellant's statements, Bibby clearly illustrates that within the cancer art cancer art there is not a clear correlation between murine and xenograft models and *in vivo* efficacy.

With regard to Point 16, Peterson et al. was cited to buttress the point that within the cancer art there is not a clear correlation between *in vitro* and xenograft data and clinical efficacy. As set forth above, Peterson et al. teaches numerous agents have show exciting activity

in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

With regard to Point 17, the disclosure of the specification and the post-filing references are limited to the efficacy of VSV against hematopoietic cell lines in *in vitro* and xenograft models. As set forth in the rejection, these results do not correlate with *in vivo* efficacy in an immunocompetent animal.

With regard to Point 18, Winograd was published in 1987. Since that time, the deficiencies of the *in vitro* assays and xenograft models with regard to their correlation to *in vivo* (clinical) efficacy has been established (as set forth in the rejection).

With regard to Point 19, the fact that the FDA typically accepts positive tumor xenograft results as a sufficient level of preclinical activity when approving a clinical trial is not an indication that there is a correlation between said results and clinical efficacy. Given the fact that few, if any drugs, have been shown to have clinical efficacy during said clinical trials, one would conclude that there is no correlation between said data and clinical efficacy.

With regard to Point 20, while *in vitro* experiments continue to be used as an initial screening method when identifying treatments for *in vivo* use, the results of said experiments do not correlate with clinical efficacy.

With regard to Point 21, aside from the fact that the prosecution of another application is not germane to the prosecution of the instant case, the rejection under 35 U.S.C. 103(a) in

application 11/385,483 dealt with the *in vitro* treatment of tumor cells (which has also been indicated as being enabled in the instant application). Said rejection is set forth below.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (WO 99/18799 – IDS) in view of Coukos et al. (Clinical Cancer Research, 1999, Vol. 5, pages 1523-1537 – IDS filed on 1-7-2008).

Roberts et al. disclose methods utilizing oncolytic viruses to treat (kill) neoplasms wherein said treatment comprises contacting the neoplastic tumor cells with the virus (see abstract). Roberts et al. further disclose that the oncolytic virus can be vesicular stomatitis virus (see page 21 and Table 1) and that VSV was capable of tumor cell specific killing (i.e. VSV selectively infects tumor cells deficient in IFN responsiveness and not "normal" cells)[see page 26, first paragraph]. Moreover, Roberts et al. disclose that their methods could be used to treat melanomas (see page 30, last paragraph).

Roberts et al. differ from instant invention in that they do not disclose the use of cells (i.e. producer cells) for the delivery of the oncolytic virus.

Coukos et al. disclose the use of producer cells for the delivery of oncolytic HSV-1 to tumor cells (see abstract). Moreover, Coukos et al. disclose that the use of producer cells may have many advantages over direct injection methods. Said advantages include: 1) amplification of viral load; 2) delivery of a virus within a producer cell may enable the virus to elude the subjects immune system; 3) use of producer cells with a binding affinity for the tumor cells would increase the localization of virus delivery; and 4) a vaccine antitumor response in selective patients might be generated (see page 1536).

Consequently, it would have been obvious to one of skill in the art to use producer cells, as disclosed by Coukos et al., in the method of melanoma tumor cell treatment disclosed by Roberts et al. One would have been motivated to due so in order to receive the benefits associated with the use of producer cells, as disclosed by Coukos et al. and cited above. One of ordinary skill in the art would necessarily have a reasonable expectation of success since both methods utilize oncolytic viruses to treat tumor cells. Moreover, given the success of using carrier cells to deliver oncolytic HAV-1, it would have been obvious for the skilled artisan to try and adapt said system to other oncolytic virus (e.g. VSV) types. Finally, given that the use of VSV as a cancer treatment is well known in the art yielding predictable results, it is obvious for the skilled artisan to use the VSV of Roberts et al. (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

Moreover, the claims in application 11/385,483 were rejected under 35 U.S.C 112, first paragraph, as not being enabled for the *in vivo* treatment of tumor cells using VSV.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Robert A. Zeman/

Primary Examiner, Art Unit 1645

Conferees:

/Robert B Mondesi/

Supervisory Patent Examiner, Art Unit 1645

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646